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Disease-a-Month

The Solitary Pulmonary Nodule

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IN RECENT YEARS there has been a complete reversal of attitudes regarding the solitary pulmonary nodule. Less than two decades ago, a "spot on the lung," a poor term but one still widely used by the general public, was viewed with almost complete complacency. If it provoked any concern at all, it was because

the lesion might represent an active focus of tuberculosis. Usually, the most that was advised was that the lesion be followed by serial roentgenograms to determine its stability. Gradually, as the disastrous results of such an ultraconservative approach became apparent, the more sinister aspects of these nodules received increasing attention in the medical literature, often under the inappropriate title of "coin lesion." To the radiologist, the lesion now constitutes a recurring problem, possibly the one encountered most frequently; in each instance, his immediate concern must be not with its infectious but with its malignant potentiality. Many, but by no means all, practicing physicians are now cognizant of the grave responsibility involved in the management of the patient with this lesion. Instead of a program of observation, prompt diagnostic thoracotomy should be, and usually is, advised. Even so, we continue to see a large number of nodules improperly managed. All too often, patients are referred for surgery only after months or years of observation, by which time the tumor is likely to be large and unresectable. The question, far from being resolved, actually seems to have been compounded by the increasing number of routine and survey chest roentgenograms.

In 1947, prompted by the widespread indifference toward, and casual disregard for, these small, innocuous-looking, asymptomatic solitary pulmonary lesions, and more directly by the distressingly late stages in which so many patients were finally being considered for surgery, one of us (E. W. D.) reported the original study (36) of this particular entity; he pointed out the high incidence of malignancy, the inability to differentiate radiographically between benign and malignant lesions (unless calcification was demonstrable) and the need for early thoracotomy. Similar reports soon appeared and subsequently many others, including several of our own. Generally speaking, these have emphasized the theme of the original paper and have called attention to other aspects of the problem—e.g., the good prognosis when an asymptomatic solitary nodule proves to be a resectable bronchial carcinoma, the adequacy of limited resections, the low surgical risk for such lesions, the nontuberculous nature of most so-called "tuberculomas" and the reliability of calcification within the nodule as an indication of benignity. Although the major argu-

ment has long been settled, the many minor controversial issues that remain, plus the continuing magnitude of the problem 5 years after our last report, seem to justify the following further reassessment.

DEFINITION.—Case selection is based on the following criteria:

1. The nodule must be 6 cm. or less in diameter. Larger nodules are excluded unless previous roentgenograms show a nodule to have been smaller than 6 cm. when initially detected.

2. The nodule must be solitary, although small satellite lesions do not preclude its inclusion.

3. It must appear to lie within the parenchyma of the lung; this excludes hilar, mediastinal, diaphragmatic and chest-wall masses. Minor pleural involvement has not been considered grounds for exclusion.

4. The nodule must be round or ovoid in shape.

5. Its margins must be circumscribed and its contour smooth. Extreme sharpness of outline has not been required.

6. Calcium or cavitation within the nodule must be minimal. When calcification is questionable or consists of a small nidus or a few flecks of calcium, the lesion can be included. The same is true of nodules containing a relatively small and insignificant area of cavitation.

7. If there is an associated pneumonitis, atelectasis or regional lymphadenitis, it must be minimal.

8. Usually, these lesions are asymptomatic, but absence of symptoms is not required for inclusion in the category of solitary pulmonary nodule.

TERMINOLOGY.—In the earliest reference to these lesions, they were described as a "spot on the lung." Fortunately, this term never gained general medical acceptance. On the other hand, "coin lesion" has become a very popular term despite the fact that these nodules, unlike a coin, retain their spherical shape in all radiographic projections. Thus, to anyone accustomed to reading lateral, as well as posteroanterior, roentgenograms, the term "coin lesion" strikes a discordant note and should be discarded.

How, then, shall we refer to these lesions? Innumerable terms have been suggested—for example, solitary intrapulmonary tumors, solitary lung tumors, isolated pulmonary nodules, single

circumscribed intrathoracic densities, circumscribed discrete pulmonary lesions, circumscribed solitary lung lesions, asymptomatic isolated intrathoracic nodules, solitary circumscribed lesions of the lung, solitary circumscribed intrathoracic radiopacities, solitary pulmonary lesions, spherical lesions of the lung, asymptomatic isolated pulmonary nodules, solitary discrete pulmonary densities, circumscribed peripheral shadows of the lung and nodular densities in the lung (27). Such a total lack of uniformity is confusing, to say the least. For that reason we would strongly urge acceptance of the term "solitary pulmonary nodule," which is our own preference because of its simplicity and specificity.

ANALYSIS OF COMBINED SERIES.—At the time of the initial report of 40 resected solitary pulmonary nodules in 1947 (36), there was no comparable series in the medical literature. Later we were able to present a comparative study between our first 67 patients, reported in 1950 (37), and the next 67 consecutive patients operated on for a solitary tumor of the lung (38). The fact that these two groups proved to be so similar has served to dispel much of the doubt as to the accuracy of our previous observations; yet there has always remained some question about the ratio of malignant to benign lesions. In our two series, the incidence of malignancy has been almost 50%, whereas in a few series it is supposedly less than 10%. It is our personal conviction that such a discrepancy stems largely from the willingness of some surgeons to resect calcified nodules. Had we chosen to do this, our total number of cases would have more than doubled and the percentage of malignant nodules would have been reduced by at least 50%.

With so much variation among different series, one way to obtain a fair estimate is to combine all reported series into one series of 2,546 cases (Table 1). This large number of cases provides statistical significance by combining reports from military hospitals, where the patients are relatively young, with those from civilian hospitals, where the patients are older, and by combining series from which partially calcified lesions have been conscientiously excluded with series weighted with calcified lesions. Also, the higher rate of malignancy introduced in some series by the inclusion of larger tumors should be more than offset by the inclusion of calcified and cavitary lesions in other series.

TABLE 1.—ANALYSIS OF REPORTED SERIES: NUMBER OF CASES*

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Lesion	O'BRIEN et al 1946	EGGER et al 1948	MASON & FORBES 1950	SHARP & WHISELLA 1950	HOUFFELDT & CARLSEN 1950	ABELES & EHRLICH 1951	EFFLER 1951	HARE & BATTERSBY 1952	BELL & SEALY 1952	WOLPAW 1952	CONDON 1952	STOREY et al 1953	JONES et al 1953	DEARS 1953	MAY et al 1954	GOBBEL & CLEVE 1954	NECKSTROTH et al 1954	WILSON & CHANG et al 1954	WILKINS 1955	HIGGINSON & HINSHAW 1955	AXTMAYER & EHRLICH 1955	JONES & BORTONE 1955	FRENCH et al 1956	CHERNIAK 1956	PAULSON 1956	SEMMITS 1956	DAVIS et al 1956	GOOD & WILSON 1956	TAYLOR et al 1956	HIBMA & BOLDON 1956	ANDERSEN et al 1958	REES et al 1958	CARTWRIGHT et al 1959	PERASALO et al 1959	Totals	
BRONCHIAL Carcinoma	8	1	2	11	18	5	6	1	8	6	17	4	25	15	8	1	11	1	27	5	2	2	4	8	62	99	79	61	18	2	26	30	95	81	739	29%
BRONCHIAL ADENOMA	1		1	2	1	1		1	3	2			12	2					2	1				2	9	3	9	10	3			4	13	3	84	
PRIMARY SARCOMA	1	1	1		1						1		1				2								3	2						1	1	6	21	
LYMPHOMA		1		1													2								1		1						1	2	9	
METASTATIC TUMOR		1	1	3	2	1	1	1	1	2		3	17	1	4		12		6	1	1			2	7	9	10	25	2	1	2	6	7	7	136	
total malignant	**9**	**4**	**5**	**17**	**11**	**8**	**7**	**3**	**12**	**10**	**18**	**7**	**55**	**18**	**12**	**1**	**27**	**1**	**35**	**7**	**3**	**2**	**4**	**12**	**79**	**114**	**101**	**96**	**23**	**3**	**28**	**41**	**117**	**99**	**989**	**39%**
GRANULOMA	8	7	48	21	2	5	8	2	10	10	2	30	65	16	18	10	29	8	20	19	6	4	22	5	67	18	82	58	183	18	13	31	146	41	1032	41%
HAMARTOMA	1	1	2	6	5	1	1			2	4	2	25	4	3	2	7		11	9		1	3	5	5	10	9	12	8		2	4	20	7	172	
BRONCHOGENIC CYST	1	6		8	4				1		1		4	9		1	3		4	2		1		7		16	6	6	12			4	2	6	104	
CHRONIC PNEUMONITIS								1					1	4								1	7			6	4	4	2				5	3	38	
NEUROFIBROMA		1				1								5					1	1						16	2			1					28	
ECHINOCOCCUS CYST		1		1										15								1		7		1									26	
MESOTHELIOMA													3						3						5		6	4	2	1		2			26	
CHRONIC ABSCESS	2				1	2							1													2	2		2		3		4		19	
A-V ANEURYSM											1				1										1	2						2	1	1	9	
FIBROMA				2							1						3									1								1	8	
BRONCHIECTATIC CYST						1																1		3										1	6	
LIPOID GRANULOMA						1													1								1						1		4	
HEMANGIOMA		1			1								1				1																		4	
LYMPH NODE		1																	1								1					1			4	
THYMOMA						1					1		1																						3	
LIPOMA														1							1														2	
XANTHOMA-MYXOMA												1		1																					2	
MISCELLANEOUS											1		3	2					1						23	24	1	4	4	1	6				70	
total benign	**12**	**18**	**50**	**38**	**13**	**12**	**9**	**3**	**11**	**14**	**9**	**33**	**101**	**58**	**24**	**13**	**43**	**8**	**42**	**32**	**6**	**9**	**32**	**27**	**101**	**96**	**114**	**88**	**213**	**21**	**24**	**44**	**179**	**60**	**1557**	**61%**
TOTAL CASES	**21**	**22**	**55**	**55**	**24**	**20**	**16**	**6**	**23**	**24**	**27**	**40**	**156**	**76**	**36**	**14**	**70**	**9**	**77**	**39**	**9**	**11**	**36**	**39**	**180**	**210**	**215**	**184**	**236**	**24**	**52**	**85**	**296**	**159**	**2546**	

*For sources, see References at end of article.

In the combined series, 39% of the nodules were malignant (Table 2). Three quarters of the malignant nodules were primary bronchial carcinomas, or 29% of all cases. The bronchial carcinomas and the bronchial adenomas together constituted 32% of the total. On this basis, 1 in 3 solitary pulmonary nodules can be expected to be a malignant or a potentially malignant bronchial tumor. Making certain allowances for the patient's age, one can estimate that practically 40% of all solitary pulmonary nodules will be malignant; about 30% will be bronchial carcinomas.

TABLE 2.—SUMMARY OF ANALYSIS OF REPORTED SERIES: PERCENTAGES

Lesion	%
BRONCHIAL CARCINOMA	29
METASTATIC TUMOR	5 1/3
BRONCHIAL ADENOMA	3 1/3
other PRIMARY MALIGNANT TUMORS	1 1/3
total malignant	39
GRANULOMA	41
HAMARTOMA	7
BRONCHOGENIC CYST	4
other BENIGN TUMORS	2 1/2
miscellaneous	6 1/2
total benign	61

The most common lesion in the combined series was the granuloma, 41% of all nodules being of this type. Most of these lesions were inadequately studied, so that more specific identification of the type of granuloma was impossible in the over-all series. Of the various benign tumors, the hamartoma was the most frequent, having been present in 172 cases (6.8%).

Two other points warrant comment: the unusually high number of echinococcal cysts in two series (14, 24), one series of cases from Australia, the other from Canada; the many neurofibromas in another series (26), presumably because of poor case selection and failure to exclude mediastinal tumors from the series.

ANALYSIS OF AUTHORS' SERIES.—Our own experience with a series of 215 solitary pulmonary nodules was reported in 1956 (27). These tumors, carefully selected according to the radiologic criteria outlined earlier, are tabulated in Table 3. These figures do not represent the total number of cases seen, for we have always regarded the partially calcified nodule as relatively innocuous and have been content merely to observe most of the lesions. We are convinced that the exclusion of calcified and cavitary lesions from this series accounts for the higher percentage of malignancies

TABLE 3.—AUTHORS' SERIES OF 215 SOLITARY PULMONARY NODULES*

LESION		CASES
Bronchial carcinoma		79 (36.3%)
Squamous carcinoma	34	
Adenocarcinoma	27	
Bronchiolar carcinoma	9	
Undifferentiated carcinoma	9	
Bronchial adenoma		9
Fibrosarcoma		1
Leiomyosarcoma		1
Lymphoblastoma		1
Metastatic tumor		10
Total malignant		101 (47%)
Granuloma		82 (38.1%)
Tuberculoma	12	
Histoplasmoma	39	
Histoplasmic lymph node	1	
Coccidioma	5	
Nonspecific	14	
Not studied	11	
Hamartoma		9
Pleural mesothelioma		6
Chronic pneumonitis		4
Bronchogenic cyst		3
Bronchopulmonary sequestration		3
Neurofibroma		2
Chronic lung abscess		2
Lipoid granuloma		1
Hyperplastic lymph node		1
"Aspergilloma"		1
Total benign		114 (53%)

*Adapted from Davis, E. W.; Peabody, J. W., Jr., and Katz, S.: J. Thoracic Surg. 32:728, 1956.

in our group. As investigators from the Mayo Clinic have shown (13), the percentage of malignancy in their series rose from 35 to 42% simply by excluding those nodules with radiographically demonstrable calcification.

Of our 215 patients (Table 3), 101 (47%) had malignant lesions. Ten of these lesions were metastatic, but the remaining 91 (42%) were primary pulmonary neoplasms. Nine were bronchial adenomas, which, in keeping with their low-grade malignant propensities, have been classified with the malignant tumors. The remainder include: 79 bronchial carcinomas, 1 fibrosarcoma, 1 leiomyosarcoma and 1 lymphoblastoma.

On the benign nodules (Table 3), 82, or more than two thirds, were granulomas. By carefully applying special stains, it has been possible to establish a specific cause in four fifths of the cases. Histoplasma was demonstrated in 40, or over one half, of all the granulomas so studied. Coccidioides was found in 5 cases, and tubercle bacilli in 12. Two of the latter cases actually represented blocked tuberculous cavities and *Mycobacterium tuberculosis* was easily recovered in culture. Despite exhaustive examination, no organisms could be identified in 14 cases, and so these were classified as nonspecific. Tissue was no longer available in 11 cases, and these were classed simply as granulomas.

There were 17 benign tumors in the series. The most common benign tumor (and this has also been true of combined reported series) was the hamartoma.* We have excised 9 hamartomas, 2 of them from 1 patient in operations spaced 5 years apart. We have found that pleural mesotheliomas frequently give the radiographic impression of an intrapulmonary location; on 6 occasions, we have operated for solitary pulmonary tumors only to find mesotheliomas. Earlier in our experience these were classified as fibromas. Two intrapulmonary neurofibromas complete the list of benign tumors.

Bronchogenic cysts were encountered 6 times; and 3 of these, all located in the right lower lobe, proved to be examples of

*Hamartoma (from the Greek, meaning "failure or error") refers to an abnormal mixing of the normal tissue components of an organ. In the lung, hamartomas contain a haphazard arrangement of the usual bronchopulmonary tissues, including cartilage, glandular and lymphoid elements. Because of the tendency of the cartilage to predominate, these tumors were once commonly referred to as "chondromas."

bronchopulmonary sequestration. Four nodules consisted of nothing more than areas of chronic pneumonitis. Two were found to be chronic lung abscesses. Despite careful study, no causing agent could be demonstrated. Of the remaining 3 patients, one had a localized lipoid granuloma, another a hyperplastic subpleural lymph node and the third a healed upper lobe cavity filled with a "fungus ball," a so-called "aspergilloma."

Our youngest patient was 18 years old; our oldest, 76. As one might predict, the patients with bronchial carcinoma were somewhat older than those with other lesions. However, the difference was not so great as in other series. In our group of 79 patients with bronchial carcinomas, 9 were in the 30–39-year age group, the youngest being 32. In keeping with reports of the type of carcinoma seen in young people, there was a disproportionately large number of undifferentiated tumors and adenocarcinomas, only 2 of the 9 being squamous carcinomas. In this same age group, our series contained 3 other malignant tumors, making a total of 12 malignant tumors, as compared with 27 benign nodules in patients of comparable age. This is significant, because some investigators believe that the chance of malignancy in solitary nodules in patients less than 40 years of age is extremely low. Yet in our experience the possibility of a nodule being malignant in the 30–39-year age group was found to be almost 1 in 3. In the 40–49-year age group, the chance of malignancy was practically 50%, and it was even higher in the older patients. Those with a bronchial adenoma had essentially the same age distribution, although 2 of these patients, aged 18 and 27, represent the youngest patients with malignant tumors in this series (Fig. 1).

The distribution of the benign lesions in the various age groups was as expected. The granulomas were fairly evenly distributed, with the largest number (22) occurring in the 30–39-year age group. In the 20–29-year age group, most of the patients (9 out of 13) had granulomas. The oldest patient in whom a benign tumor was removed (a hamartoma) was a man of 74. The remainder of the benign nodules were too evenly distributed to be of any statistical significance.

In the entire series, only 81 patients (37.6%) were women. Among those with granuloma, there was almost an even breakdown between women (42) and men (40); the same was true

of bronchial adenoma (4 out of 9 patients were women), metastatic tumor (5 out of 10 were women) and hamartoma (4 out of 9 were women). There was a predominance of females among the patients with pleural mesothelioma (4 out of 6 were women); but in those with bronchial carcinoma, 64 out of 79 (81%) were

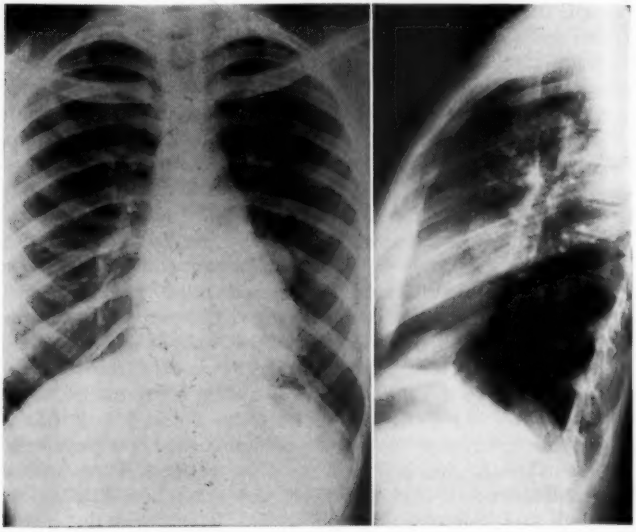

FIG. 1.—Routine chest roentgenograms of a girl, aged 18, revealing a 3.5/cm. nodule in the left midlung field. At thoracotomy a bronchial adenoma of the carcinoid type was resected. Having done well since operation, this patient provides an excellent illustration that youth provides no assurance against a potentially malignant lesion.

men. Needless to say, in any given case the patient's sex cannot be relied on to rule out the possibility of malignancy.

The lobar distribution of the nodules was fairly even, with no great difference between the malignant and benign tumors. Since all cases represented circumscribed peripheral lesions, location likewise appeared to have no effect on prognosis.

Symptoms, their presence or absence and their significance, are difficult to evaluate in the patient with a solitary pulmonary nodule (Fig. 2). Initially, most of our patients denied having any symptoms; but, when closely questioned, a number admitted a slight cough. This was a more common finding in the patient with bronchial carcinoma. It should be recognized, however, that 25 patients with bronchial carcinoma were observed for periods ranging from 1 to 8 years before being referred to us for surgical

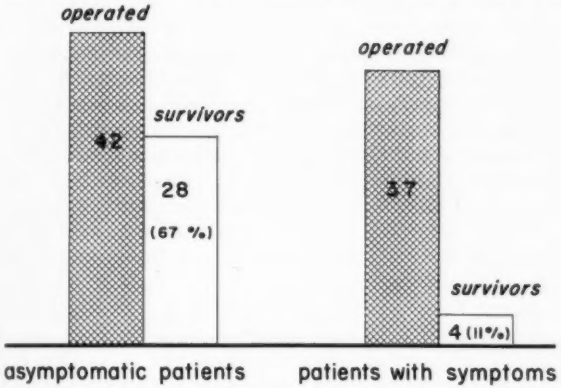

FIG. 2.—Relation of symptoms, or lack of symptoms, to survivorship, based on 79 resected bronchial carcinomas.

consultation. Of these, a certain number had been asymptomatic when the nodule was originally discovered but had developed symptoms while under observation. Other patients developed symptoms after being advised of an abnormality in their chest roentgenogram. This was especially true of chest pain, which was usually of a mild, fleeting nature. When the complaint was one of definite, persistent chest pain, as it was in 6 patients in our series, it invariably indicated a malignant process. Some history of pain might be anticipated with the granulomas, for almost all of these were situated subpleurally and were associated with an overlying area of pleural thickening. In this connection, the group from the Mayo Clinic (13) found that, of 65 patients with granuloma, 12 had some degree of chest pain. This has not been

true of our patients; and we suspect that the Mayo report included instances of vague, momentary pains which we have disregarded in our report.

Hemoptysis was a symptom with definite diagnostic significance. Eleven of our patients had coughed up blood in varying quantities, the sputum usually being only blood streaked. Eight of these patients proved to have bronchial carcinoma, and another one had a bronchial adenoma; among those with benign lesions, there were only 2 patients with hemoptysis, and they had a chronic nonspecific type of pneumonitis. One other symptom was most dramatic when it occurred and, in this series, was indicative of a malignant lesion; this was severe arthralgia involving one or more joints with associated clubbing of the digits. It is well known, of course, that such symptoms are frequently associated with bronchial carcinoma and that they are much more commonly associated with peripheral lesions, especially when there is pleural involvement. Three of our patients had severe arthralgia, and all 3 had bronchial carcinomas. One lesion was invading the pleura; the other two were immediately subpleural in location. None of our pleural mesotheliomas was accompanied by pulmonary osteoarthropathy; this is surprising because this tumor is supposed to have the highest incidence of arthralgia and clubbing, although in total frequency it ranks second to bronchial carcinoma. In our experience, the occurrence of arthralgia in association with bronchial carcinoma has an unfavorable prognosis; all 3 of our patients with this finding were dead at the time of our last report (27).

DIAGNOSIS

Probably the point of paramount importance in the over-all problem of the solitary pulmonary nodule is the customary inability to identify the precise nature of any particular nodule by any method other than thoracotomy. It is true, of course, that clinical and laboratory data may suggest certain diagnostic possibilities or may, in a negative sense, prove helpful by lending a sense of urgency to a diagnostic thoracotomy. Still, such data rarely, if ever, provide information sufficient to obviate the need for surgery.

HISTORY.—Seldom does the patient's history provide a reliable clue to a preoperative diagnosis. At times it may even be misleading, especially for the patient with an asymptomatic malignant lesion who at some time in the past has been exposed to, or has actually had, active tuberculosis. It is impossible to overemphasize the fact that *an absence of symptoms is no assurance that a solitary pulmonary nodule is benign.* Contrariwise, the presence of thoracic symptoms secondary to the nodule, while admittedly favoring malignancy, in no way eliminates the possibility of a benign lesion.

Reference has been made to the manner in which a history of tuberculosis can serve as a "red herring" and mask the malignant nature of a nodule. To presume that the nodule is tuberculous is quite tempting and in most instances constitutes the logical diagnostic choice; but, however strong the history, there is still too little certainty to justify a program of medical observation. Too many of these presumed "tuberculomas" turn out to be malignant. Similarly, a history of a previously treated extrapulmonary carcinoma may provide an important clue that one is dealing with a metastatic nodule. Yet one must always be reminded that the lesion in the lung may represent an entirely independent process, either malignant or benign. This is no better illustrated than in our own series, in which 3 patients who had previously had malignant lesions excised from other areas proved to have primary bronchial carcinomas.

PHYSICAL EXAMINATION.—Seldom does the physical examination contribute to the diagnosis of a solitary pulmonary nodule. Nevertheless, it certainly should not be omitted, for it does permit an evaluation of the patient's general state of health, besides providing a means for searching for a primary carcinoma elsewhere. Breast, kidney, thyroid, colon and ovary are the most frequent primary sites of carcinoma associated with a solitary metastasis to the lung. Likewise, the presence of a melanoma or the scar resulting from its removal should not be ignored. The same is true of other evidence of metastasis, such as regional lymphadenopathy or an enlarged nodular liver.

Another significant finding is the presence of a murmur or bruit over the approximate site of a pulmonary nodule, for this strongly suggests a pulmonary arteriovenous fistula. Telangiectases

over the skin, lips and other mucous membranes also tend to support the vascular nature of a pulmonary nodule.

LABORATORY EXAMINATION.—Routine laboratory studies are of no diagnostic significance. The value of the sedimentation rate is disputed; some investigators regard an elevated sedimentation rate as an indication of malignancy but others disagree. Certainly, in our hands the sedimentation rate has not been particularly helpful.

SKIN TESTS AND SEROLOGIC TESTS.—Skin and serologic tests, although they are made routinely in these patients, have no positive diagnostic value. A positive test, for example, does not prove that the lesion in question is responsible for the positive reaction. Neither do negative tests absolutely exclude any etiologic possibility. However, if the reactions to a properly performed test are negative on three occasions, the specific organism will not be demonstrable in the resected specimen. In fact, the lack of response to the three major skin antigens—tuberculin, histoplasmin or coccidioidin—lends an even greater sense of urgency to the prospective thoracotomy. This is the chief properative value of skin testing; but, in addition, skin tests are most helpful in deciding which staining technics should be employed in identifying the causative organism following the resection of a granuloma.

BACTERIOLOGIC EXAMINATION OF SPUTUM.—Examination of sputum, and of gastric and bronchial washings for tubercle bacilli and fungi by smear is so rarely productive that, in general, this procedure is of little aid in diagnosis. Cultural methods occasionally give positive reactions. Even if tubercle bacilli are found, the coexistence of tuberculosis and carcinoma cannot be excluded. Therefore, considering the low yield of cultures in encapsulated tuberculous foci, the delay related to this technic of examination, the significance of false positive and false negative cultures and the urgency of surgery for the indistinguishable case of carcinoma, there is rarely any justification for delaying operation until cultures are reported.

CYTOLOGIC EXAMINATION.—The peripheral location of malignant lesions does not preclude finding malignant cells in the sputum, for in one series as high as 74% of the cases yielded tumor cells (26). A negative report certainly does not eliminate carcinoma from consideration. The latter fact, the occasional un-

reliability of a positive report and—most important—the failure of either a positive or negative report to alter the decision to operate have tempered the enthusiasm for cytologic studies. The last statement might be modified by some in the extremely poor-risk patient in whom there might be justification for surgery in the presence of overwhelming evidence that the nodule is malignant.

BRONCHOSCOPY.—Because these nodules are peripherally situated, bronchoscopy is seldom helpful. At times, a nodule close to a visible segmental orifice may be diagnosed bronchoscopically. Bronchoscopy may also be useful in securing washings for cytological study.

BRONCHOGRAPHY.—Although some investigators have found bronchography of value, the majority opinion is unenthusiastic. Failure of the contrast medium to enter a nodule is no assurance of its malignant nature.

ASPIRATION BIOPSY.—This diagnostic technic is rarely indicated to prove the cause of a solitary nodule. This is not to deny that diagnostic tissue may be obtained at times in the subpleurally located nodule. However, the danger of spreading the tumor, of infection, of bronchopleural fistula and of hemorrhage has made this method unpopular. Furthermore, negative results do not eliminate the possibility of malignancy. In the patient with a fairly large peripheral lesion, with evidence of pleural symphysis, and in whom surgery is contraindicated, aspiration biopsy may be performed in order to obtain tissue to justify the use of x-ray therapy or cancer chemotherapy.

SCALENE NODE BIOPSY.—In the absence of significant mediastinal lymphadenopathy, this type of examination has been unproductive in the work-up of a patient with a pulmonary nodule. However, in the poor-risk patient, scalene node biopsy is useful, for, when positive, it contraindicates further surgical intervention.

ROENTGENOGRAPHY.—Because this lesion is usually detected radiographically and since almost all diagnostic measures are unrewarding, painstaking and refined attempts at diagnosis have followed roentgenologic lines. Many features related to the radiologic appearance have been analyzed in the hope of defining the cause of the pulmonary nodule. Although most of the measures fail to achieve this, they do offer clues worthy of recognition.

Size.—A moment's reflection will quickly dispel the complacency generally stimulated by the very small pulmonary nodule, for every large carcinoma was once tiny. In general, nodules less than 1.0 cm. are more likely to be benign and larger nodules (over 4 cm.) are more apt to be malignant. But most of the solitary nodules are between 1 and 4 cm. in diameter, and herein lies the dilemma. However, in an individual case, size cannot be used as a guide to the nature of, or to the biologic activity of, a nodule (Fig. 3). Frequently, in a patient with a large solitary primary malignant nodule, we have obtained roentgenograms made months, or even years, previously and have observed a small nodule, the radiographic beginning of the carcinoma, which was either overlooked or disregarded because it was small and the patient was asymptomatic.

Sharpness of margin.—To base a diagnosis in any given case on the general impression that benign nodules have a more sharply defined border is likely to prove disastrous, for there are too many exceptions to this rule. The presence of linear drainage bands extending from the nodule to the hilum is seen more often in granulomatous lesions, but again cannot be considered pathognomonic.

Umbilication of margin ("notch sign").—The appearance of umbilication or an indentation on the surface of a solitary nodule favors the likelihood of malignancy. This is especially true with reference to the larger nodules. Exceptions to this observation (some granulomas and hamartomas) are sufficiently frequent, however, to limit its value. In addition, false notch signs may occur, owing to superimposition of blood vessels and other structures. Regardless of the validity of this sign, its value as a guide to therapy must be questioned, because cases in which it is positive usually warrant surgical management anyhow. What is needed, instead, is a roentgenologic aid that would spare the patient unnecessary surgery.

Recent origin.—When previous x-rays are available to attest to the origin of a pulmonary nodule within a matter of months, malignancy is suggested. On the other hand, some granulomatous nodules may have been present at the time the earlier films were made but were not visible roentgenographically. Sometimes within a few months, as organization, fibrosis and mineral-salt deposition

FIG. 3.—Roentgenographic example demonstrating the fallibility in attaching diagnostic significance to the size of a pulmonary nodule. The small circumscribed lesion in *A* measured less than 1 cm. in diameter but proved, at operation, to be a bronchial carcinoma. By contrast, the bulky lesion in *B*, measuring almost 6 cm. in diameter, turned out to be a granuloma containing Histoplasma (histoplasmoma).

ensue, the nodule may become more apparent, although it does not represent a new lesion.

Growth.—Rapid, concentric growth of a solitary pulmonary nodule is usually indicative of malignancy (Fig. 4). As is true of most radiographic guides, however, this sign is also replete with exceptions, inasmuch as benign lesions, especially granulomas, may behave similarly. As indicated in the previous paragraph, this often represents "x-ray growth" rather than anatomic growth. Slow, almost imperceptible growth, on the contrary, is no war-

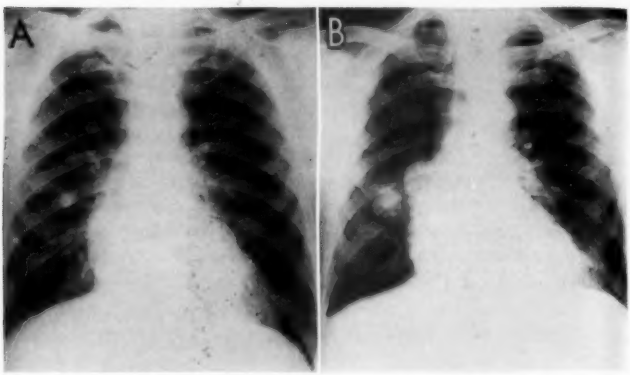

FIG. 4.—A routine chest roentgenogram *(A)* of a man, aged 59, revealed a 2-cm. nodule in the right midlung field. Three years later *(B)*, the nodule showed concentric enlargement associated with marked hilar lymphadenopathy. Despite a recent coronary thrombosis, operation was advised. An extensive squamous carcinoma was encountered, but the patient has remained well for nearly 4 years following pneumonectomy.

ranty of the benign nature of a lesion. Since one can be deluded by an apparently stable lesion, justifiable assurance of benignity should demand that the lesion be unchanged for at least 5 years.

Density.—Too much reliance should not be placed on the density of a pulmonary nodule as a reflection of the presence or absence of calcium. A dense lesion is not necessarily calcified. More significance can be given to the density of a solitary nodule when the density is also related to size. Thus, although not an absolute rule, nodules under 2 cm. and dense are commonly

granulomas, while those of similar size but not dense may be either granulomas or carcinomas. Those over 2 cm. and dense may be either granulomas or carcinomas, while those of this size but not dense are probably carcinomas. It should be understood that these clinical tenets, although helpful, are not sufficiently reliable to control the management of solitary pulmonary nodules.

Satellite nodules.—Frequently at the time of surgery, small subpleural satellite nodules are noted about a solitary granuloma. These are usually not apparent on x-ray. However, when seen in the roentgenogram, such small satellite densities usually indicate that the major pulmonary nodule is benign. Again, this is not an infallible sign.

Cavitation.—Small radiolucent areas within a solitary nodule may represent cavitation, necrosis or merely a difference in radiodensity compared with the major portion of the nodule. In some series, nodules of this variety are excluded from consideration because of the assumption that they are benign (an erroneous concept) and because a cavitary nodule is usually accepted as an indication for surgery. However, since the solitary nodule with radiolucent zones presents the same problems as the homogeneous nodule, it may logically be included.

Some nodules that appear solid initially may show signs of necrosis at a later date. Such lesions may be benign or malignant. Malignancy is suggested when the radiolucency is eccentrically situated, consists of multiple small zones or is surrounded by a ragged wall. Cavitary nodules may represent granuloma, carcinoma, fungus ball, (or "aspergilloma"), bronchogenic cyst, bronchopulmonary sequestration or chronic lung abscess.

Calcification.—The most important part of the roentgenographic examination is the demonstration of calcification and a clear delineation of its pattern. Why? Because the demonstration of calcium within a solitary pulmonary nodule decidedly, but not absolutely, suggests benignancy.

It is essential that the presence of calcium be unquestionable, since it is known that the assessment of calcium in the roentgenogram is often difficult. In this connection, the use of tomography is essential. To serve as a useful sign, not only must the calcium be shown to lie within the nodule, but the calcific deposit must not be just one of many similar deposits in the same area. Otherwise,

one cannot be sure that the calcification did not antedate a more recently evolving tumor in the same area. Needless to say, previous x-rays may be most helpful in evaluating this possibility. It must be conceded that the presence of a few tiny flecks of calcium within a pulmonary nodule cannot be construed as firm evidence of a benign lesion.

Of paramount importance is the type of calcification, for the pattern of the calcification has more meaning in regard to benignity than has its mere presence. Lesions which are diffusely stippled with calcium, lesions presenting a calcific inner or outer ring or concentric laminations of calcium or those containing a large central calcific core or total calcification are almost assuredly benign. Bizarre and eccentric patterns of calcification may be seen in calcifying or ossifying bronchial adenoma, and this variety of calcification is therefore not listed among the favorable varieties. Calcification has been noted, not only in granuloma and hamartoma, but also in hematoma, parasitic infestations and metastatic osteogenic sarcoma.

THORACOTOMY.—Thoracotomy must be listed as a diagnostic aid because it is usually the only method by which the etiological identification of a solitary nodule can be established (Fig. 5). At exploration, total removal (biopsy) not only provides the diagnosis but likewise is, in many instances, the treatment of choice.

The absence of any mortality due to exploration and limited resection alone, the reasonably low mortality rate following more radical resection and the absence of any appreciable morbidity, except in cases of carcinoma and tuberculosis, where it might be anticipated anyway, provides, to our way of thinking, convincing proof of the safety in exploring every patient with a solitary, noncalcified pulmonary nodule. In all of our cases the magnitude of the resection was dictated by a correlation of the patient's condition, the gross findings at operation and the results of frozen-section tissue examination. In 8 cases, all of them unresectable carcinomas observed for more than 1 year prior to surgical consultation, the operative procedure was limited to exploration and biopsy. In all of the other cases, the lesions were resectable—a limited resection if benign, and either pneumonectomy or lobectomy if malignant. As will be pointed out later, under the discussion of bronchial carcinoma, we have come to regard lobectomy

as adequate treatment for many of the peripheral carcinomas unassociated with gross involvement of the lymph nodes. Finally, the fact that pneumonectomy was performed for 11 benign lesions deserves explanation. This simply reflects the fact that early in our experience we were less adept at distinguishing

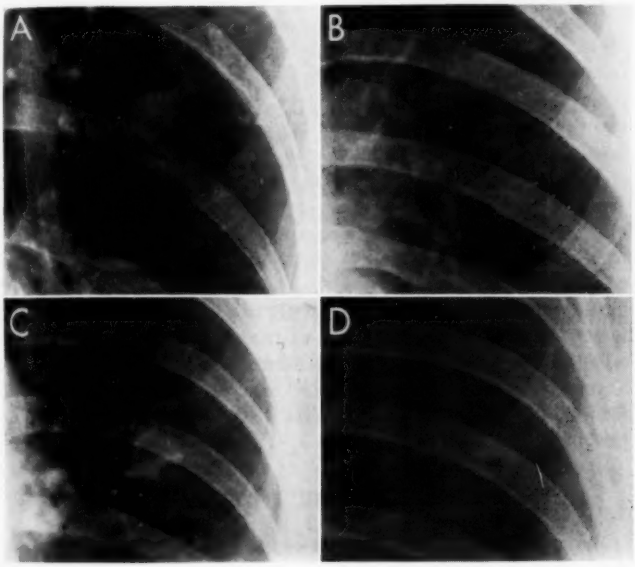

FIG. 5.—Spot roentgenograms of 4 solitary pulmonary nodules closely resembling each other in size, shape and location but differing completely as to cause. One is a bronchial carcinoma *(D)*; but to differentiate clinically between this and the other three *(A, B* and *C)* cannot be done by any method other than thoracotomy.

between benign and malignant tumors and considered pneumonectomy to be the only adequate operation for bronchial carcinoma.

Our mortality rate with thoracotomy plus a limited resection (108 cases) has been nil. However, among the patients with lobectomies and pneumonectomies (107 patients), there have been

5 hospital deaths, 4 after pneumonectomy and 1 following lobectomy; the pathologic diagnosis in each case was bronchial carcinoma. Another patient with a large granuloma died at home suddenly and unexpectedly 6 weeks following pneumonectomy. He, too, has been included as an operative death, bringing the total for the series to 6 deaths (2.8%).

The morbidity rate has been correspondingly low. Early in the series, there were 5 cases of bronchopleural fistula with empyema following pneumonectomy. All the lesions eventually healed after pleural drainage and thoracoplasty. During the last 8 years of this study, there have been but 2 cases of empyema, both following pneumonectomy, and both patients responded to aspiration plus combined systemic and intrapleural antibiotic administration. Two patients, after wedge resection of supposedly nonspecific granulomas, developed tuberculous reactivation and required long-term chemotherapy plus completion of the lobectomy. Finally, one other case, following a wedge resection for a nonspecific granuloma, was complicated by a persistent bronchopleural fistula which responded to completion of the lobectomy and long-term antituberculous chemotherapy, although a tuberculous origin was never established. Except for these cases, all patients did well and were discharged from the hospital on an average of 8–10 days postoperatively.

PATHOLOGIC ENTITIES

Bronchial carcinoma.—The outstanding single entity among the solitary pulmonary nodules is the bronchial carcinoma. Indeed, only because of these localized primary malignant tumors does the subject of the solitary pulmonary nodule achieve special significance. Besides being the most important kind of pulmonary nodule, bronchial carcinoma also rivals the granuloma as being the most common. From a combined analysis of reported series, bronchial carcinoma has been shown to account for 29% of all solitary nodules (Table 2). In our experience, the incidence is higher, amounting to 37% of 215 cases (Table 3); the difference in incidence probably stems from the fact that calcified lesions have never been included in our own statistics.

The various cell types of the carcinomas in the combined series occur in approximately the same numbers as those generally ascribed to all varieties of peripherally arising bronchial carcinomas. Of 79 such tumors in our series, 36 were adenocarcinomas, 34 were squamous carcinomas and the remaining 9 were of the undifferentiated type. While the latter figures are quite different from those of bronchial carcinoma in general, only about 13% of which are adenocarcinomas, it is fairly representative of other studies, demonstrating that primary adenocarcinomas arise predominantly in the periphery of the lung. Nine of our 36 adenocarcinomas were of the bronchiolar or "alveolar cell" type.

Regarding survival, it is worth noting that in an earlier report we stated that "the end results are somewhat surprising, for they suggest, though admittedly in figures far short of statistical significance, that the adenocarcinomas and undifferentiated carcinomas have as favorable a prognosis as the squamous variety" (27). Since then, this finding has become even more apparent, owing to the deaths of 3 of the early survivors with squamous carcinoma,

TABLE 4.—Survivorship in 79 Cases of Bronchial Carcinoma (Authors' Series)

Cell Type	No. of Patients	Survivors
Squamous carcinoma	34	12 (35%)
Adenocarcinoma	36	16 (44%)
Undifferentiated carcinoma	9	4 (44%)
Total	79	32 (40%)

but, as far as we can determine, the loss of only 1 additional patient with adenocarcinoma. Thus, the 5-year survival for the entire group amounts to 32 patients (40%) (Table 4). However, 1 patient with squamous carcinoma, who was treated by pneumonectomy and whose hilar nodes were free of any detectable metastic involvement, lived 5 full years before showing evidence of recurrence. Another patient with a squamous carcinoma lived 11 years postoperatively before dying of spinal metastasis. All told, there are currently 16 survivors out of 36 with adenocarcinoma (44%), 12 out of 34 with squamous carcinoma (35%) and 4 out of 9 with undifferentiated carcinoma (44%). Interestingly enough, this very point was previously emphasized by

Belcher (35), who found, after an elaborate study, that patients with bronchial adenocarcinoma amenable to lobectomy seem to have a better prognosis than those with squamous carcinoma similarly situated. Even greater emphasis is cast in this direction if the bronchiolar carcinomas are excluded, for of the remaining 27 patients with adenocarcinomas, 14 survive (52%). On the other hand, we have only 2 survivors out of 9 patients operated on for bronchiolar carcinoma. We cannot help but conclude that the bronchiolar carcinomas hold the least favorable prognosis. As we stated earlier, regardless of their small, asymptomatic nature, their characteristic lack of nodal involvement and the fact that on microscopic examination they seem better differentiated than the average adenocarcinoma, these lesions hardly warrant the appellation "favorable bronchiolar carcinoma," as they have been designated by Overholt and his co-workers (39).

Along the same lines, there has recently appeared a splendid analysis of 94 cases of bronchial carcinomas presenting as a solitary nodule (41). Adenocarcinoma, squamous carcinoma and large-cell carcinoma each accounted for about 30% of the 94 lesions. Of those patients followed for 3 years or longer, there was an over-all 3-year survival rate of 36.6%. Nine of the patients proved inoperable because of extensive mediastinal metastases. When these patients are excluded, the survival rate rose to 44.7%. Deletion of the 8 unresectable cases in our own series raises our over-all 5-year survival rate from 40 to 45%, which is a remarkably similar result.

In reviewing our own material, it soon became apparent that a discouragingly large number of patients had been observed for excessively long periods before being considered for thoracotomy. Thus, in an earlier report (27), we found that, of the 43 patients who were already dead, 28 had been observed by their physician for periods in excess of 6 months, and that 20 of these had actually had the growth of their nodule checked periodically for longer than 1 year. We believe that such a policy cost many of these patients their only chance for cure.

Whether the patients were symptomatic or not seemed to influence survival. Among our original 79 patients with primary carcinomatous nodules, 65 were asymptomatic when the lesion was initially discovered. During the prolonged periods of observa-

tion forced on so many of these patients, 23 additional patients developed symptoms of one sort or another before being operated on. By the time of thoracotomy, 37 patients had symptoms, whereas 42 had none. Analysis of these two groups reveals what is, to us, the most significant finding in this study. Of the 42 asymptomatic patients, 28 are alive and apparently well, representing an extremely gratifying survivorship of 66.6%. Sharply contrasting with this group are the 4 survivors out of 37 patients operated on after the appearance of symptoms (10.8% survival). Thus, one can anticipate a satisfactory outcome in two thirds of the patients with asymptomatic nodules but in only 1 out of 10 of those patients with symptoms secondary to their tumor.

Moreover, there has been a rather clear-cut relationship between the existence of symptoms and mediastinal lymph-node involvement. Whereas only 5 patients (12%) of those without symptoms showed microscopic evidence of involvement of mediastinal lymph nodes, 27 (67.5%) of the symptomatic group exhibited metastatic tumor in one or more mediastinal lymph nodes. Eight of the latter patients were inoperable. Conversely, the asymptomatic lesions were uniformly resectable. This is not unexpected, of course, and coincides with other reports on asymptomatic nodules, at least in the broad sense that the asymptomatic lesion has a higher rate of resectability and logically should provide a higher rate of curability than does bronchial carcinoma associated with symptoms.

The time lapse between radiographic detection of the lesion and operation likewise seems to influence survival. In a general way, the longer the time lapse, the less likely is the chance for cure. Admittedly, the biologic behavior of the tumor is of paramount importance, as illustrated by 3 patients in our series who appear to have had curative resections despite a delay of 2-3 years between discovery of the carcinoma and its resection. This simply indicates the indolence and relatively low biologic activity of a few of these lesions, particularly among the older male patients. For the most part, however, the opposite was true. Forty-two patients were operated on within 6 months following detection of the nodule, and 24 survive in apparent good health (57%). When operation was delayed 6 months to a year, there were only 3 survivors among 12 patients (25%). When opera-

tion was postponed over 1 year, as it was in 25 patients, only 5 patients survived 5 years. Likewise, one should not forget the many other patients who, in a similar period of observation, have developed signs of inoperability and have died of their disease without any chance of surgery and are, therefore, never considered in reviews of this sort.

Our experience has convinced us that *the patient with a small solitary asymptomatic bronchial carcinoma recently detected in a routine chest roentgenogram has a surprisingly good chance for permanent cure if operated on promptly.* Thirty-two of our patients met these requirements, and 21 (66%) survive in apparent good health. We would be the first to admit that the series is too small to assume statistical significance, but it still suggests that 2 out of 3 patients with silent bronchial carcinomas so situated and so handled will survive 5 years.

Finally, it is highly significant that the extent of surgery (pneumonectomy versus lobectomy) does not appear to have any significant effect on the ultimate survival of certain cases, and we now regard lobectomy as a perfectly sound and adequate operation in properly selected cases, the chief requirements being a well-circumscribed lesion, peripherally situated and free of gross lymph-node involvement.

The surgical procedures performed on the 79 patients with bronchial carcinoma consisted of pneumonectomy 39 times, lobectomy 30 times, biopsy 8 times, and limited resections twice, the latter having been prompted by erroneous frozen-section diagnoses. Of the 32 survivors, 17 had had pneumonectomies and 15 had had lobectomies; in other words, slightly less than one half of the original patients with pneumonectomy and exactly one half of the patients with lobectomy survive. To us, the feature of greatest significance is the fact that those who died of recurrent carcinoma following lobectomy died not of local recurrence but of generalized metastases, most often cerebral. Thus, the trend in our management of these patients has changed from routine pneumonectomy to lobectomy whenever feasible. When no gross evidence of lymph-node involvement has been noted and the lesion was confined to the periphery of a lobe, our long-term results with lobectomy have been as good as those with pneumonectomy, and the mortality and morbidity rates have been decidedly less.

On the other hand, we do not mean to imply that lobectomy is a satisfactory substitute for pneumonectomy in less favorable situations. When the tumor encroaches on the hilus or when enlarged hilar or mediastinal lymph nodes are present, we consider pneumonectomy to be the treatment of choice.

BRONCHIAL ADENOMA.—The subject of bronchial adenomas brings up two important points: (1) the question of malignancy; and (2) the not infrequent, although seldom appreciated tendency to arise peripherally.

That all bronchial adenomas are potentially malignant is well known. To be convinced of this, one has but to witness the lymphatic and sometimes more extensive recurrence following local excision of an apparently benign lesion, or to encounter frank carcinomatous transformation in an otherwise benign adenoma. Considering how difficult it may be to prove the origin of a carcinoma from an adenoma, this last possibility may occur more commonly than we think. For these reasons, we regard all bronchial adenomas—carcinoids or cylindromas—as low-grade adenocarcinomas with an exceedingly favorable outlook if excised early but with a guarded and often fatal prognosis if ignored. Since no one would dispute the need for their excision, it seems justifiable to classify them as malignant lesions.

That they are not exclusively hilar lesions likewise needs to be elaborated on, because the well-recognized form of the bronchial adenoma is an obstructive tumor, not a peripheral solitary nodule. Actually, about 10% will arise far enough peripherally to present the radiographic appearance of a solitary nodule. Nine nodules in our series turned out to be bronchial adenomas, an incidence of 4%, which is somewhat higher than the incidence in most series but only half that reported from the Mayo Clinic (13).

Surprisingly, 5 of the adenomas in our series occurred in men and only 4 in women. There were 6 carcinoids, 2 cylindromas and 1 well-differentiated mucous-gland adenoma. There was lymph-node involvement in but 1 case, and all 9 patients remain alive and well, all for periods in excess of 5 years.

RARE PRIMARY PULMONARY MALIGNANCY.—Little need be said about the many malignant tumors that occasionally develop in the lung and still less commonly present as a solitary nodule. Representative examples, such as fibrosarcoma, a leiomyosarcoma and a

lymphoblastoma, are included in our series. The subject of bronchopulmonary sarcoma has been elaborately reviewed by Iverson (42), who has drawn special attention to the rarity of these tumors and to their peripheral location, predominance in middle-aged persons, difficulties in pathologic differentiation and amenability to surgical excision. A number of entities — both malignant, such as oat-cell and pleomorphic-cell carcinoma, and benign, for example, postinflammatory pseudotumors—are likely to be mistaken for pulmonary sarcoma, thus emphasizing the need for care in microscopic interpretation.

METASTATIC MALIGNANCY.—The distinction between a primary malignant nodule and a metastatic nodule cannot always be made, even by histologic study. Obviously, then, one could hardly expect roentgenographic differentiation of these two entities.

A solitary pulmonary nodule in a patient who has or has had a malignant lesion is not necessarily related to the known malignant process. Instead, it may also represent a benign nodule or another primary malignant lesion (Fig. 6). This is the chief reason for advocating prompt thoracotomy in a patient with a solitary pulmonary nodule and a history of a previously excised extrapulmonary carcinoma. This approach is especially desirable if a prolonged interval separates the initial carcinoma and the appearance of a solitary pulmonary nodule.

As a routine preoperative measure, an extensive roentgenographic search for a subclinical primary extrapulmonary tumor does not seem justifiable. Without some hint of the primary site, the yield is low; and the direct surgical approach appears more logical, less time consuming and certainly less expensive in the long run. This is not to deny that pyelographic studies and gastrointestinal series will occasionally reveal an unsuspected primary carcinoma to which the pulmonary lesion is secondary, and these studies should certainly be carried out, if a careful review of systems suggests the presence of a primary tumor elsewhere.

The ratio of multiple metastatic pulmonary nodules to solitary metastases is about 100:1. Characteristically, once a metastatic nodule appears in the lung, additional metastatic lesions to the lung and other organs soon follow. However, this statement is not invariably true; the presence of metastases in the lung does not necessarily indicate the existence or imminence of widespread

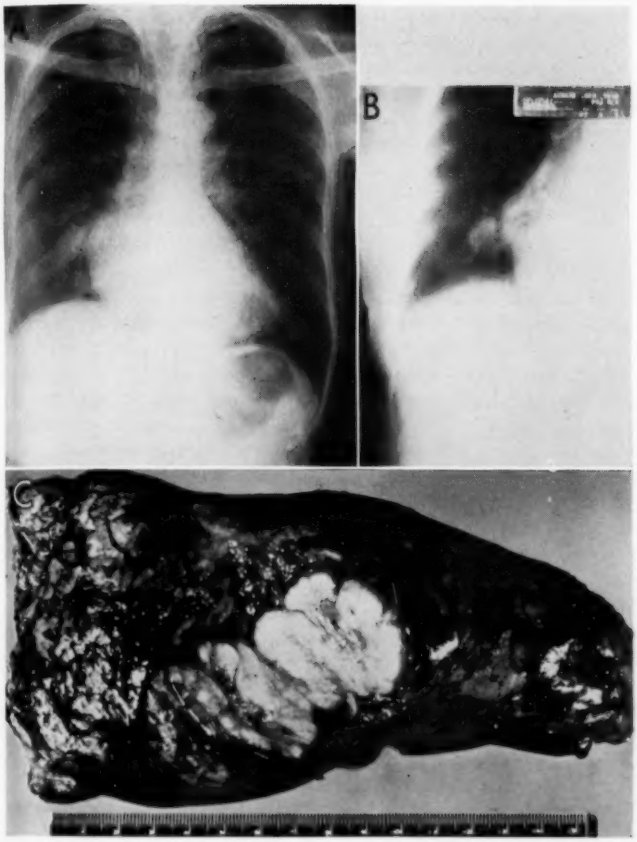

FIG. 6.—Routine chest roentgenograms *(A* and *B)* of a woman, aged 70, showing a 3.5-cm. nodule in the right lower lobe. Note the absence of the left breast, which had been removed 5 years earlier for carcinoma. Right lower lobectomy *(C)* demonstrated a primary bronchiolar carcinoma. The patient is apparently well 3 years later.

metastasis. Although the merits of resecting a metastatic pulmonary nodule may appear dubious, in some instances the excision may prolong life, even for extended periods. The essential requirements for such an approach are reasonable assurance that the primary tumor has been controlled and the absence of other sites of metastases. Ideally, 3 years or so should have elapsed between control of the primary carcinoma and the appearance of the secondary. It is true that this last criterion is somewhat specious, for the logic in delaying surgery on the "metastatic" nodule for this time interval is nullified by the fact that the nodule may represent a primary bronchial carcinoma.

Other conditions, such as cell type, organ of origin, extent and speed of growth of the primary and secondary lesion and invasive characteristics of the primary tumor, may affect the outcome of surgery for a metastatic pulmonary nodule. Nevertheless, these factors do not consistently influence the chance for cure. In actual practice, the likelihood of surgery on a metastatic pulmonary nodule is slight (about 1% of metastatic pulmonary neoplasm), for although resection may be technically feasible, other conditions—e.g., an uncontrolled primary site, other metastases and the poor general condition of the patient—preclude surgery. In general, the prospects for surgery are best for metastases due to carcinoma of the skin, cervix, colon, kidney, ovary and breast, and they are better for metastatic sarcoma than for metastatic carcinoma. A long interval may intervene between the removal of a malignant melanoma or renal cell carcinoma and the presence of a metastatic pulmonary nodule; but frequently on the heels of this metastatic event, other metastases, pulmonary and extrapulmonary, soon appear.

GRANULOMA.—In the group of solitary pulmonary nodules known as granulomas, a characteristic, although often nonspecific, histologic reaction is produced. No matter how suggestive the pathologic picture, specific identification depends on the precise recognition of the causative agent. At times, identification is not possible, and the designation "nonspecific granuloma" is used—an admission that the hallmark of the granulomatous reaction may remain without the demonstration of the cause.

In almost every series of solitary pulmonary nodules—certainly in those reported from this country—the most common single en-

tity has been the granuloma. It accounts for the majority of the benign lesions and represents 41% of all solitary nodules (Table 1). In the past, a great deal of confusion and unnecessary anxiety have stemmed from the fact that the terms tuberculoma and granuloma have been used interchangeably. This is neither desirable nor justifiable, for this etiologic assumption has too often been based simply on finding a caseating or noncaseating granuloma. Even when soft or cavitary, such granulomatous foci generally show no tubercle bacilli on smear, culture or by special acid-fast staining of the histologic preparations. When the nodules are fibrotic or partially calcified, the bacteriologic yield is almost negligible. In this situation, if only the tuberculin test is positive, the presumptive diagnosis of tuberculoma appears justifiable. However, when the tuberculin test is negative, it is illogical to incriminate the tubercle bacillus.

It has long been recognized that the residual lesion of coccidioidomycosis may be represented as a solitary pulmonary nodule. The simplicity of establishing this diagnosis may perhaps be attributed to the ease with which sporangia are identified even without special staining methods. In contrast, proof of the histoplasmic nature of a solitary pulmonary nodule is more elusive because of the infinitely greater difficulty in demonstrating Histoplasma in clinically quiescent foci. With the application of newer and more specialized staining procedures, the diagnosis of histoplasmosis has become more secure. The "histoplasmoma" represents a healing and, at times, healed primary parenchymal focus of histoplasmosis; and in these lesions, Histoplasma stains poorly, or not at all, with hematoxylin and eosin. However, with special stains, such as periodic acid-Schiff (PAS), Gridley or Gomori methenamine-silver nitrate, Histoplasma is often readily identified. Re-examination of tissue blocks by these stains has revealed that 55% of the granulomas studied contain Histoplasma and 7% Coccidioides, in contrast to only 17% in which a tuberculous origin could be established. In addition, there are granulomas due to silicosis, to brucellosis and to lipoid pneumonia.

The prognosis of solitary granulomas is difficult to appraise and must be individualized. With known tuberculomas, there is a constant threat of reactivation. In general, they respond well to antituberculosis chemotherapy; but when they excavate or en-

large, surgical resection is a wiser choice of therapy. When the tuberculoma represents a blocked cavity rather than an encapsulated pulmonary focus which has never excavated, resection may also be justified. However, in many instances the precise pathogenesis of a tuberculoma cannot be established. The main factor involved in the decision to excise a nodule eventually proved to be tuberculous is the inability to exclude malignancy. Rarely does a calcified tuberculoma undergo excavation or account for reactivation and bronchogenic spread.

If the mycotic etiology of a nodule can be assured, surgery is, as a rule, not indicated. Cavitation may occur within the solid coccidioidal residuum but is less frequent in a histoplasmoma. In either situation, dissemination is most unlikely. In histoplasmoma, the organisms are seldom viable, judging by the great difficulty in culturing *Histoplasma capsulatum* from the specimen.

One major practical concern is the patient with a resected granulomatous nodule in whom an etiological identification cannot be established. If the tuberculin test is positive and tuberculosis cannot be excluded, antituberculosis chemotherapy is indicated as a precautionary measure to prevent future reactivation. We feel very strongly about this, having had 2 patients develop recurrent cavitary disease due solely to our failure to institute such chemoprophylaxis.

HAMARTOMA.—Hamartomas are considerably more common than is generally thought. In the above-mentioned Mayo Clinic series, for example, hamartomas were as frequent as bronchial carcinomas at one time, comprising 16% of all solitary nodules (13). It is interesting to note that in a recent report by the same group of investigators decidedly different statistics were obtained, the number of hamartomas being 12, as compared with 61 bronchial carcinomas of a solitary nodular type operated on during the same period (28). Nine hamartomas are included in our series, and 2 of these were resected from the same patient in operations performed 5 years apart. Malignancy is an extremely rare development in a hamartoma, and for practical purposes this possibility can be dismissed.

PLEURAL MESOTHELIOMA.—It is sometimes surprising to see how often a solitary fibrous type of pleural mesothelioma conveys the radiographic impression of a pulmonary nodule, when in real-

ity the lesion is extrapulmonary. One of the major problems in categorizing the various solitary pulmonary nodules is the difficulty in differentiating localized pleural mesotheliomas from fibromas, fibrosarcomas, neurofibromas and neurofibrosarcomas, for any of which the nodules can be mistaken. Clubbing of the digits and arthralgia are frequent accompaniments of this tumor but were noted in none of the mesotheliomas in this series. Even when present, such signs provide no help in ruling out bronchial carcinoma. Moreover, regardless of their benignity, mesotheliomas warrant excision on their own merits because of the tremendous size they may ultimately achieve.

UNRESOLVED PNEUMONITIS AND ABSCESS.—Occasionally, a chronic inflammatory process will assume the configuration of a fairly well-defined pulmonary nodule. Since such a process is likely to be accompanied by symptoms such as hemoptysis and because the margin of this kind of nodule is likely to be slightly hazy, it may more strikingly resemble carcinoma than will the average nodule.

BRONCHOGENIC CYSTS.—Bronchogenic cysts without functional communication with a bronchus can distend with mucus or pus and thus assume the appearance of a pulmonary nodule. It was of interest to us that, out of 6 such cysts presenting as a solitary nodule that we have encountered, closer scrutiny showed that 3 had an anomalous blood supply from the aorta, and this threw them into the category of intralobar bronchopulmonary sequestration.

RARE PRIMARY BENIGN PULMONARY LESIONS.—The benign pulmonary lesions which, in rare instances, present as solitary pulmonary nodules are almost too numerous to mention. They include an occasional neurofibroma, fibroma, hemangioma, arteriovenous fistula, leiomyoma, lipoma and even thymoma. Once again, histologic differentiation may be quite difficult.

SUMMARY

This report represents a further reassessment of the solitary pulmonary nodule. Our own series of 215 personally resected, noncalcified pulmonary nodules correlates well with the literature in illustrating both the strong malignant propensity of these nodules and the improbability of distinguishing between the benign and the malignant lesion by any means short of thoracotomy.

Thus, in our series, 47% of the lesions were malignant (37% were bronchial carcinomas). Of 2,546 cases collected from the world literature, 39% were malignant (29% of all cases were bronchial carcinomas). Clinical, laboratory and roentgenologic data have been elaborately analyzed without finding any sign reliable enough to justify medical observation, unless it be calcification within the nodule. Even this may be hazardous, so that minimal calcification can no longer be regarded as proof of benignity. A mere fleck of calcium within the nodule is not enough. There remain certain patterns of calcification that render the possibility of malignancy so remote, however, that further observation seems warranted. These include those nodules with a large central calcific core or diffuse calcific stippling, those with an inner ring or outer rim of calcium and, of course, those that are completely calcified.

Two outstanding categories among the solitary nodules are the bronchial carcinomas and the granulomas, which together comprise 75% of all nodules. Of special interest are the prognosis of the primary malignant nodules and the etiological identification of the granulomas.

In determining survival of the patients with bronchial carcinoma, cell type appeared to have far less influence than did either the presence of symptoms or the lapse of time between radiographic discovery of the lesion and operation. Our findings indicate that the patient whose small solitary circumscribed asymptomatic bronchial carcinoma was recently detected in a fortuitous chest x-ray has a 66% chance of surviving 5 years *if operated on promptly*. Lobectomy appears to be an adequate operation in properly selected cases of cancer.

Early in our experience, all of the solitary granulomas, because of their gross appearance, if nothing else, were presumed to be "tuberculomas." Re-examination of the tissue blocks in these cases by special staining technics has been most revealing. Fifty-five per cent of the granulomas studied contained Histoplasma and 7% contain Coccidioides, in contrast to but 17% in which a tuberculous origin could be established.

In conclusion, we feel that every solitary, noncalcified pulmonary nodule demands thoracotomy, that for the patients with bronchial carcinoma the absence of symptoms and promptness of

surgery are likely to determine the chance for cure and that careful histologic study of the pulmonary granulomas will reveal the majority of nodules to be of fungal rather than tuberculous origin.

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